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| 10/632,711 | 08/01/2003 | Dennis A. Carson | 02307O-124010US | 2786 |

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| EXAMINER | |
|---|---|
| GRAFFEO, MICHEL | |
| ART UNIT | PAPER NUMBER |
| 1614 | |

DATE MAILED: 08/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/632,711 | CARSON ET AL. | |
| | Examiner | Art Unit | |
| | Michel Graffeo | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-41 and 51-58* is/are pending in the application.

4a) Of the above claim(s) *9-13, 18-20, 27-34, and 39-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,14-17,21-26,35-38 and 51-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Action*

Claims 1-8, 14-17, 21-26, 35-38 and 51-58 are examined.

Applicant has provided arguments for the patentability of claims 1-8, 14-17, 21-26, 35-38 and 51-58 in the response filed 3 May 2006.

Applicant's arguments, see response, filed 3 May 2006, have been fully considered but are not persuasive. Any rejection not specifically stated in this Office Action has been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Claim Rejections - 35 USC § 103*

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,358,855 to Markovic et al. in view of US Patent No. 5,405,837 to Weber, further in view of Chen et al. Evaluation of mizoribine as an immunosuppressant in subrenal capsule assay using immunocompetent mice. Japanese Journal of Cancer Research: Gann, (1990 Feb)81 (2) 183-7 and further in view of Leoni et al. Indanocine, a Microtubule-Binding Indanone and a Selective Inducer of Apoptosis in Multidrug-Resistant Cancer Cells. Journal of the National Cancer Institute, Vol. 92, No.3 (2000).

Markovic et al. teach specifically that IMPDH inhibitors, such as tiazofurin and mycophenolic acid, have been used as cancer chemotherapeutic treatments (in current claims 1,3; see col 1 lines 19-28).

Markovic et al. do not specifically teach the use of mizoribine for example together with an α-tubulin polymerization inhibitor such as indanocine.

Weber teaches the treatment of cancer comprising tiazofurin in concert with a second component (in current claims 1-8; see col 2 lines 6-14) such as ribavirin (another chemotherapeutic agent).

Chen et al. teach that mizoribine, a IMPDH inhibitor (see page 186 second column), effectively reduces the size of tumors (in current claims 1-8; see Fig. 2 on page 185).

Leoni et al. teach that indanocine has antiproliferative activity (in current claim 5; see especially Background) in for example, breast cancer (in current claims 6-8; see Discussion on page 222).

One of ordinary skill in the art would have been motivated to combine the above references and as combined would teach the invention as claimed. One of ordinary skill in the art would have been motivated to combine the above references primarily because Weber teaches that tiazofurin, an IMPDH inhibitor, should be used in conjunction with another agent. Moreover, all four references are directed to chemotherapeutic agents (Chen et al. and Leoni et al. cited to show the knowledge of mizoribine and indanocine in the art) and combining agents which are known to be useful as chemotherapeutics individually into a single composition useful for the very

same purpose is *prima facie* obvious. See In re Kerkhoven 205 USPQ 1069. Since it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining an IMPDH inhibitor and an α-tubulin polymerization inhibitor flows logically from their having been individually taught in the prior art. Thus, the combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,358,855 to Markovic et al. in view of US Patent No. 5,405,837 to Weber, further in view of Chen et al. Evaluation of mizoribine as an immunosuppressant in subrenal capsule assay using immunocompetent mice. Japanese Journal of Cancer Research: Gann, (1990 Feb)81 (2) 183-7 and further in view of Uckun et al. Biology and Treatment of Childhood T-Lineage Acute Lymphoblastic Leukemia. Blood, (91);, 1998. 735-746.

Markovic et al. teach specifically that IMPDH inhibitors, such as tiazofurin and mycophenolic acid, have been used as cancer chemotherapeutic treatments (in current claims 14-17; see col 1 lines 19-28).

Markovic et al. do not specifically teach the use of mizoribine for example together with a precursor of Ara-GTP such as guanine arabinoside (Ara-G).

Weber teaches the treatment of cancer comprising tiazofurin in concert with a second component (in current claims 14-17; see col 2 lines 6-14) such as ribavirin (another chemotherapeutic agent).

Chen et al. teach that mizoribine, a IMPDH inhibitor (see page 186 second column), effectively reduces the size of tumors (in current claims 14-18; see Fig. 2 on page 185).

Uckun et al. teach that Ara-G is selectively cytotoxic for T-cell lines and T-lineage leukemic cells (in current claims 14-18; see page 741 bottom if first column).

One of ordinary skill in the art would have been motivated to combine the above references and as combined would teach the invention as claimed. One of ordinary skill in the art would have been motivated to combine the above references primarily because Weber teaches that tiazofurin, an IMPDH inhibitor, should be used in conjunction with another agent. Moreover, all four references are directed to chemotherapeutic agents (Chen et al. and Uckun et al. cited to show the knowledge of mizoribine and Ara-G in the art) and combining agents which are known to be useful as chemotherapeutics individually into a single composition useful for the very same purpose is *prima facie* obvious. See In re Kerkhoven 205 USPQ 1069. Since it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining an IMPDH inhibitor and a precursor of Ara-GTP flows logically from their having been individually taught in the prior art. Thus, the

combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

Claims 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,358,855 to Markovic et al. in view of US Patent No. 5,405,837 to Weber, further in view of Chen et al. Evaluation of mizoribine as an immunosuppressant in subrenal capsule assay using immunocompetent mice. Japanese Journal of Cancer Research: Gann, (1990 Feb)81 (2) 183-7 and further in view of US Patent No. 5,840,505 to Carrerra et al.

Markovic et al. teach specifically that IMPDH inhibitors, such as tiazofurin and mycophenolic acid, have been used as cancer chemotherapeutic treatments (in current claims 21-26; see col 1 lines 19-28).

Markovic et al. do not specifically teach the use of mizoribine for example together with an inhibitor of the de novo pathway of purine biosynthesis such as l-alanosine.

Weber teaches the treatment of cancer comprising tiazofurin in concert with a second component (in current claims 21-26; see col 2 lines 6-14) such as ribavirin (another chemotherapeutic agent).

Chen et al. teach that mizoribine, a IMPDH inhibitor (see page 186 second column), effectively reduces the size of tumors (in current claims 21-26; see Fig. 2 on page 185).

Carrerra et al. teach a method of treating cancer, for example cancer cells that are deficient in MTAP activity (in current claim 26; see Abstract), with L-alanosine ( in current claims 21-26; see col 1 lines12-20).

One of ordinary skill in the art would have been motivated to combine the above references and as combined would teach the invention as claimed. One of ordinary skill in the art would have been motivated to combine the above references primarily because Weber teaches that tiazofurin, an IMPDH inhibitor, should be used in conjunction with another agent. Moreover, all four references are directed to chemotherapeutic agents (Chen et al. and Carrerra et al. cited to show the knowledge of mizoribine and inhibitors of de novo purine biosynthesis) and combining agents which are known to be useful as chemotherapeutics individually into a single composition useful for the very same purpose is *prima facie* obvious. See In re Kerkhoven 205 USPQ 1069. Since it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining an IMPDH inhibitor and inhibitors of de novo purine biosynthesis flows logically from their having been individually taught in the prior art. Thus, the combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

Claims 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,358,855 to Markovic et al. in view of US Patent No. 5,405,837 to Weber, further in view of Chen et al. Evaluation of mizoribine as an immunosuppressant

in subrenal capsule assay using immunocompetent mice. Japanese Journal of Cancer Research: Gann, (1990 Feb)81 (2) 183-7 and further in view of US Patent Application No. 2003/0003057 to Weers et al.

Markovic et al. teach specifically that IMPDH inhibitors, such as tiazofurin and mycophenolic acid, have been used as cancer chemotherapeutic treatments (in current claims 35-38; see col 1 lines 19-28).

Markovic et al. do not specifically teach the use of mizoribine for example together with a GPCR antagonist such as leuprolide.

Weber teaches the treatment of cancer comprising tiazofurin in concert with a second component (in current claims 35-38; see col 2 lines 6-14) such as ribavirin (another chemotherapeutic agent).

Chen et al. teach that mizoribine, a IMPDH inhibitor (see page 186 second column), effectively reduces the size of tumors (in current claims 35-38; see Fig. 2 on page 185).

Weers et al. teach a method of treating cancer comprising leuprolide, a GPCR antagonist (in current claims 35-38; see Abstract).

One of ordinary skill in the art would have been motivated to combine the above references and as combined would teach the invention as claimed. One of ordinary skill in the art would have been motivated to combine the above references primarily because Weber teaches that tiazofurin, an IMPDH inhibitor, should be used in conjunction with another agent. Moreover, all four references are directed to chemotherapeutic agents (Chen et al. and Weers et al. cited to show the knowledge of

mizoribine and leuprolide) and combining agents which are known to be useful as chemotherapeutics individually into a single composition useful for the very same purpose is *prima facie* obvious. See In re Kerkhoven 205 USPQ 1069. Since it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining an IMPDH inhibitor and leuprolide flows logically from their having been individually taught in the prior art. Thus, the combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

Claims 51-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,358,855 to Markovic et al. in view of US Patent No. 5,405,837 to Weber, and further in view of Chen et al. Evaluation of mizoribine as an immunosuppressant in subrenal capsule assay using immunocompetent mice. Japanese Journal of Cancer Research: Gann, (1990 Feb)81 (2) 183-7.

Markovic et al. teach specifically that IMPDH inhibitors, such as tiazofurin and mycophenolic acid, have been used as cancer chemotherapeutic treatments (in current claims 51-58; see col 1 lines 19-28).

Markovic et al. do not specifically teach the use of mizoribine in any particular amounts.

Weber teaches the treatment of cancer comprising tiazofurin in concert with a second component (in current claims 51-58; see col 2 lines 6-14) such as ribavirin

(another chemotherapeutic agent). Moreover, Weber teaches various modes of administration (injection, infusion etc.) and dosing regimes (in current claims 51-58; see col 3 lines 32-36) greater than 4,400mg/$m^2$ (see col 4 lines25-27) or in a range between 1100-3300 mg/$m^2$ (see col 4 lines 25-28 and 44-45). Although Weber does not specifically recite administration via oral mode or parenteral, one of ordinary skill in the art would find it obvious to do so, absent evidence to the contrary. Also, absent evidence to the contrary is the teaching of such a broad range of dosing regimes for tiazofurin that one of ordinary skill in the art would appreciate and find obvious the routine optimization of dosing amounts and routes of administration for comparable IMPDH inhibitor, mizoribine, to meet the limitations of the instant claims.

Chen et al. teach that mizoribine, a IMPDH inhibitor (see page 186 second column), effectively reduces the size of tumors (in current claims 51-58; see Fig. 2 on page 185).

One of ordinary skill in the art would have been motivated to combine the above references and as combined would teach the invention as claimed. One of ordinary skill in the art would have been motivated to combine the above references primarily because Weber teaches that tiazofurin, an IMPDH inhibitor, is an effective chemotherapeutic agent. Moreover, all three references are directed to chemotherapeutic agents (Chen et al. cited to show the knowledge of mizoribine) and Markovic et al. teaching effectiveness of other IMPDH inhibitors such as tiazofurn. Thus, the combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

***Response to Arguments - 35 USC § 103***

Applicant's arguments filed 3 May 2006 have been fully considered but they are not persuasive. Applicant argues that the references fail to teach the claimed combination and in particular that Weber et al. do not teach a combination that includes a second chemotherapeutic agent for example one that inhibits a cellular process regulated by GTP. Combining agents which are known to be useful as chemotherapeutics individually into a single composition useful for the very same purpose is *prima facie* obvious. See In re Kerkhoven 205 USPQ 1069. Since it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining an IMPDH inhibitor and a second chemotherapeutic agent flows logically from their having been individually taught in the prior art.

Applicant additionally, argues that the teaching of a combination wherein the active agents have different mechanisms of actions is not taught and that the instant Specification shows unexpected results from a combination of actives having different mechanisms of action. That notwithstanding, a greater than additive effect, for example, is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. Ex parte The NutraSweet Co., 19 USPQ2nd 1586 (Bd. Pat. App. & Inter.

1991). To that extent, the same rejection applies and is proper since one of ordinary skill in the art would have expected greater efficacy with a combination of agents having different mechanisms of action over a combination of agents having the same mechanism of action.

Applicant's further argue that there is no motivation to administer a single IMPDH inhibitor for the treatment of cancer. Such limitation is not recited in the rejected claim(s).

## *Conclusion*

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michel Graffeo whose telephone number is 571-272-8505. The examiner can normally be reached on 9am to 5:30pm Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

4 August 2006
MG

Ardin H. Marschel 8/6/06
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SUPERVISORY PATENT EXAMINER